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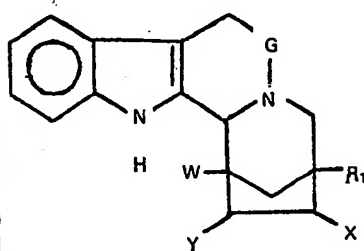
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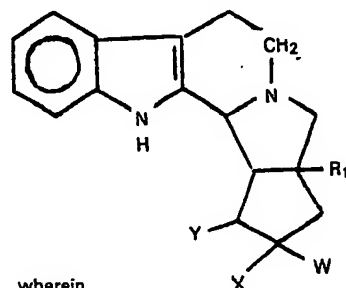
Indolo 2,3-alquinoilzine and indolo2,3-glicyclopentalindolizine derivatives.

Compounds of formulae (II)



and (III)

(II)



(III)

wherein

W is alkoxycarbonyl having from one to four carbon atoms in the alkoxy moiety or cyano,

R<sub>1</sub> is hydrogen or alkyl having from one to four carbon atoms,

G is a  $\text{>CH}_2$  or  $\text{>C=O}$  group with the proviso that, where G is a  $\text{>C=O}$  group, W is alkoxycarbonyl having from one to four carbon atoms in the alkoxy moiety and R<sub>1</sub> is hydrogen, and

X and Y each stands for hydrogen or together represent a C-C bond,

are disclosed, which compounds possess interesting gastric acid secretion inhibiting activity. Processes for preparing them and pharmaceutical compositions containing them are also disclosed.

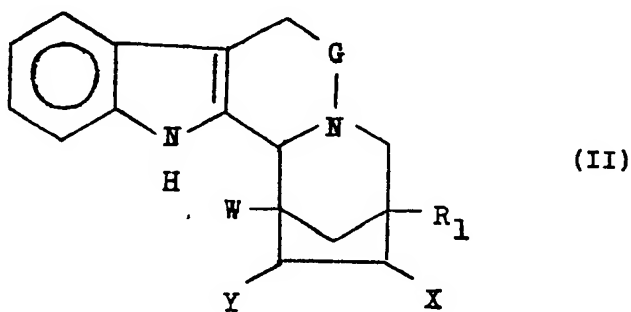
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Indolo[2,3-a]quinolizine and indolo[2,3-g]cyclopent[a]-  
indolizine derivatives

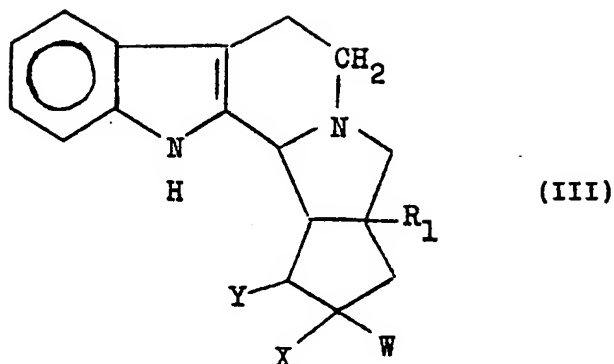
The invention relates to new indolo[2,3-a]-  
quinolizine and indolo[2,3-g]cyclopent[a]indolizine  
5 derivatives.

A structural analogue of the indolo[2,3-g]-  
cyclopenten[a]indolizines of the present invention  
has been prepared by Winterfeldt et al. [Angew.  
Chem. 89(12), 916-17 (1977)] as a key intermediate  
10 in the synthesis of eburnamonine [Chemische Berichte  
112(5), 1879-1888, 1889-1901, 1902-1912 (1979)  
and 114(5) 1932-1937 (1981)]. Cyclopent[1,2]indolizino-  
[8,7-b]indole derivatives are also disclosed in  
Org. Mass. Spektrom. 15(10), 544 (1980). The  
15 indolo[2,3-a]quinolizines of the present invention  
have, however, an entirely new structure and no  
structurally related compounds are known.

According to one feature of the present invention  
there are provided new indolo[2,3-a]quinolizines  
20 of the formula (II)



and new indolo[2,3-g]cyclopent[a]indolizines of  
the formula (III)



wherein

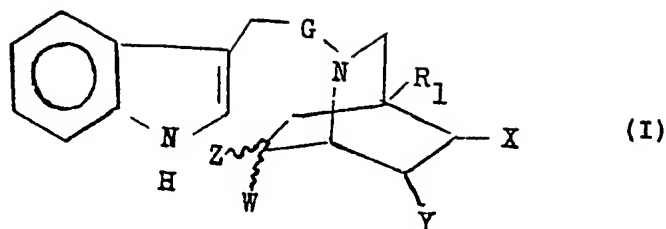
- W is alkoxy carbonyl having from one to four carbon atoms in the alkoxy moiety or cyano,  
 5  $R_1$  is hydrogen or alkyl having from one to four carbon atoms,  
 G is a  $>CH_2$  or  $>C=O$  group with the proviso that, where G is a  $>C=O$  group, W is alkoxy carbonyl  
 10 having from one to four carbon atoms in the alkoxy moiety and  $R_1$  is hydrogen, and  
 X and Y each stand for hydrogen or together represent a C-C bond.

Compounds of formulae (II) and (III) are  
 15 biologically active and in particular possess interesting gastric acid secretion inhibiting activity.

In the above formulae as an alkoxy carbonyl group having from 1 to 4 carbon atoms in the alkoxy moiety W may represent any straight or branched  
 20 chained ( $C_{1-4}$  alkoxy) carbonyl, e.g. methoxy, ethoxy, n- or isopropoxy, n-, iso- or tert.-butoxy carbonyl group.

$R_1$  may represent any straight chained or branched  $C_{1-4}$  alkyl group, e.g. a methyl, ethyl,  
 25 n-propyl, isopropyl, n-butyl, isobutyl or tert.-butyl group.

According to a further feature of the invention compounds of the formulae (II) and (III) may be prepared starting from compounds of formula (I)



in which W, R<sub>1</sub>, G, X and Y are as defined above  
and Z is halogen. Z as halogen may stand for fluorine,  
5 chlorine, bromine or iodine.

Thus, in order to prepare compounds of formula  
(II) in which G is a  $\text{>CH}_2$  group and/or compounds  
of formula (III), compounds of formula (I), in  
which G stands for  $\text{CH}_2$  (denoted herein formula  
10 (IA)) are heated in an organic solvent, and if  
desired, the mixture of compounds of formulae (II)  
and (III) obtained is subsequently separated, and/or  
the compound of formula (II) is converted into  
the corresponding compound of formula (III).

15 Compounds of formula (II) in which G represents  
a  $\text{>C=O}$  group and thus W is (C<sub>1-4</sub> alkoxy)carbonyl  
and R<sub>1</sub> is hydrogen may be prepared by reacting  
the corresponding compound of formula (I) in which  
G is  $\text{>C=O}$ , W is (C<sub>1-4</sub> alkoxy)carbonyl and R<sub>1</sub> is  
20 hydrogen (denoted herein formula (IB)) with a complexing  
agent, in an organic solvent, under anhydrous conditions.

Compounds of formulae (II) and (III) in which  
X and Y together represent a C-C bond may, if  
desired be saturated by catalytic hydrogenation  
25 to give the corresponding compound of formula (II)  
or (III) in which X and Y are each hydrogen.

When compounds of formula (I) in which G  
is a  $\text{CH}_2$  group are heated in an organic solvent  
to yield a mixture of the corresponding compounds  
of the formulae (II) and (III), the organic solvent  
30 is preferably a polar protic solvent, most preferably  
a C<sub>1-4</sub> alcohol or diethylene glycol. At lower  
temperatures, after a short period heating compounds

of formula (II) are generally obtained which may then, if desired, be converted into the corresponding thermodynamically more stable compounds of formula (III) by a longer heating at higher temperature.

- 5 Under appropriate reaction conditions compounds of formula (I) can be directly converted substantially completely into compounds of the formula (III).

Compounds of the formulae (II) and (III) may be separated from each other by column chromatography  
10 and, if desired, after isolation, compounds of the formula (II) may be converted into the corresponding compounds of the formula (III) as described above. The separation of the compounds of formulae (II) and (III) is preferably carried out by column chromatography.  
15 Any unreacted starting substance may be separated from the mixture of the compounds of formulae (II) and (III) preferably on a Kieselgel 60 column, by gradient elution techniques. The compounds of the formulae (II) and (III) themselves  
20 may then preferably be separated from each other on an  $\text{Al}_2\text{O}_3$  column, again by gradient elution techniques.

Compounds of the formula (I) in which G represents a  $\text{>C=O}$  group, due to their lower reactivity, cannot be converted into the corresponding compounds of  
25 formulae (II) and (III) by thermal means. Instead they are heated in the presence of a complexing agent, preferably silver tetrafluoroborate or silver hexafluoroantimonate, in an organic solvent, under anhydrous conditions to yield the corresponding  
30 compounds of formula (II). The compounds of the formula (II) obtained by this reaction cannot be further transformed into compounds of formula (III). Preferred solvents for this are apolar aprotic organic solvents, most preferably halogenated aliphatic  
35 hydrocarbons such as dichloromethane; aromatic hydrocarbons, e.g. benzene and toluene; and nitrobenzene.

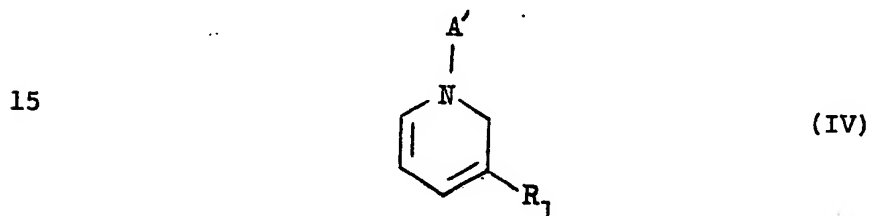
If desired, the compounds of the formula (II) or (III), in which X and Y together form a

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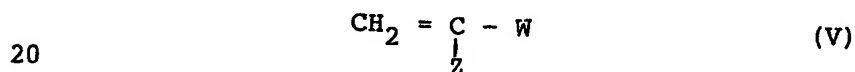
C-C bond, can be saturated in a known manner, by catalytic hydrogenation to give the corresponding compound in which X and Y are each hydrogen. Catalytic hydrogenation is preferably carried out in the presence of a palladium-on-charcoal catalyst.

The 2-azabicyclo[2.2.2]octane derivatives of formula (I) are new compounds which are described and claimed inter alia in our co-pending European Patent Application No. of even date herewith claiming priority from Hungarian Patent Application No. 2343/83.

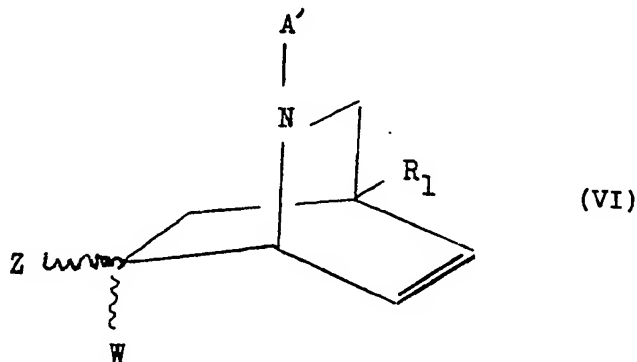
Thus the compounds of formula (I) may be obtained by reacting a 1,2-dihydropyridine derivative of formula (IV),



(in which  $R_1$  is as defined above and  $A'$  is  $(C_{1-4}$  alkoxy)carbonyl or phenyl  $(C_{1-4}$  alkoxy)carbonyl) with an acrylic acid derivative of formula (V),

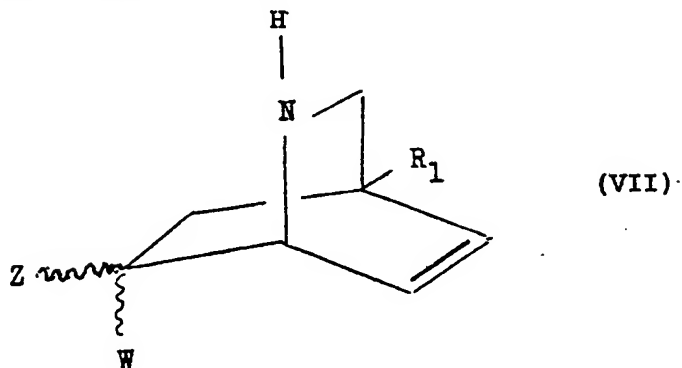


(in which W and Z are as defined above) to give a compound of formula (VI)



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(in which  $R_1$ , W, Z and A' are as defined above)  
 which may then be reacted with an acid to yield  
 a compound of formula (VII)



5 (in which  $R_1$ , Z and W are as defined above) or  
 an acid addition salt thereof which may subsequently,  
 optionally after saturation of the double bond  
 by catalytic hydrogenation, be alkylated or acylated  
 to give the desired compound of formula (I).

10 As mentioned above, the compounds of formulae  
 (II) and (III) are biologically active possessing,  
 in particular an interesting gastric acid secretion  
 inhibiting activity. Thus we have found that,  
 measuring the gastric acid secretion inhibiting  
 15 activity according to the method of Shay (Gastro-  
 enterology, 1945, 5, 43-46), the products of Examples  
 1 and 4 exhibit  $ED_{50}$ s of 25 and 20 mg/kg respectively  
 i.p. on rats. Correspondingly they exhibit  $LD_{50}$ s,  
 measured according to the method of Litchfield  
 20 and Willcoxon (J. Pharmacol. Exp. Ther., 96, 99  
 [1949]) of 250 and 200 mg/kg respectively i.p.  
 on rats.

According to a further feature of the present  
 invention there are provided pharmaceutical compositions  
 25 comprising, as active ingredient, at least one  
 compound of formula (II) or (III) as hereinbefore  
 defined, in association with a pharmaceutical carrier  
 or excipient. Such compositions may be formulated  
 according to conventional methods well known in  
 30 the art.

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The invention is elucidated in detail by  
the aid of the following non-limiting Examples.

Preparation 12-Benzoyloxycarbonyl-4-ethyl-7-chloro-7-methoxycarbonyl-  
2-azabicyclo[2.2.2]oct-5-ene

- 21.4 g (0.2 moles) of 3-ethyl-pyridine are dissolved in  
5 250 ml of absolute methanol. To the solution 7.5 g (0.2  
moles) of powdered sodium tetrahydroborate are slowly added  
below  $-65^{\circ}\text{C}$ , under vigorous stirring in argon atmosphere,  
followed by the addition of 28.8 ml (34.1 g., 0.2 moles) of  
benzyl chloroformate. The reaction is strongly exothermic.  
10 When the addition is complete, the reaction mixture is stirred  
for an additional hour, whereupon it is carefully heated up  
to room temperature. The reaction mixture is evaporated  
in vacuo. The evaporation residue is dissolved in 200 ml. of  
ether and washed with 100 ml of water. The aqueous phase is  
15 extracted with two additional 100-ml. portions of ether. The  
combined ethereal phases are washed with 20 ml. of a 1% aqueous  
acetic acid solution. The pH of the aqueous solution is  
about 5-6 after the extraction. The ethereal phase is  
dried over magnesium sulfate, and evaporated in vacuo.  
20 The evaporation residue is a mixture of N-benzyloxy-  
carbonyl-1,2-, 1,4- and 1,6-3-ethyl-dihydropyridine isomers.  
UV spectrum (methanolic solution):

$\lambda_{\text{max}}$  = 305 nm 1,2- and 1,6-3-ethyl-dihydropyridine

$\lambda_{\text{max}}$  = 260-270 nm unreacted 3-ethyl-pyridine

25  $\lambda_{\text{max}}$  = 230-240 nm 1,4-dihydropyridine.

The evaporation residue weighs 36.7 g. (0.153 moles).

IR spectrum:  $1700\text{ cm}^{-1}$  = N-C=O;  $1470\text{ cm}^{-1}$  phenyl;  $1100\text{ cm}^{-1}$   
C-O-C;  $700\text{ cm}^{-1}$ ; phenyl.

t.l.c. (Kieselgel 60 F<sub>154</sub>, eluant: 10 : 1 mixture of benzene and acetone, development: in UV light of 254 nm or iodine vapour):  $R_f = 0.84$  (1,2 and 1,6 isomers).

The evaporation residue is dissolved in 150 ml. of absolute acetonitrile, and 24.4 g. (0.194) of 2-chloro-  
5 acrylic acid chloride and 0.1 g. of hydroquinone are added to the solution. The completion of the cycloaddition is shown by the disappearance of the  $\lambda_{\max} = 305$  nm peak in the UV spectrum. Thereafter, 150 ml. of absolute  
10 methanol are added to the reaction mixture, which is then stirred at room temperature for three hours. The pH of the acidic solution is adjusted to 8-9 by addition of triethylamine under cooling, and it is then evaporated in vacuo. The evaporation residue is dissolved in 100 ml.  
15 of benzene, and washed with 50 ml. of water. The benzene phase is dried over magnesium sulfate, filtered and evaporated in vacuo. 59.9 g. of an oily product are obtained, which is then chromatographed on a Kieselgel 60 (0.063-0.2 mm.) column by using a 10 : 1 mixture of  
20 benzene and acetone as an eluant.

Yield: 19.3 g. (35 % based on 3-ethyl-pyridine).

IR spectrum (film):  $1700\text{ cm}^{-1}$  =N-O;  $1470\text{ cm}^{-1}$  phenyl;  
 $1100\text{ cm}^{-1}$  C-O-C;  $700\text{ cm}^{-1}$  phenyl.

t.l.c. (Kieselgel 60 F<sub>254</sub>, eluant: a 10 : 1 mixture of  
25 benzene and acetone, development: in UV light of 254 nm or in iodine vapour):  $R_f = 0.85$ .

Preparation 22-Benzyloxycarbonyl-4-ethyl-7-chloro-7-cyano-2-azabicyclo-  
/2.2.2/oct-5-ene

50 g. (0.2 moles) of 3-ethyl-(N-benzyloxycarbonyl)-  
5 1,2-dihydropyridine, contaminated with the 1,4- and 1,6-  
isomers, are prepared as described in Preparation 1. It is  
then dissolved in 60 g. (0.69 moles) of 2-chloroacryl  
nitrile together with 1 g. of hydroquinone. The reaction  
mixture is protected from light and stirred on an oil  
10 bath of 70 °C for 70 hours. The completion of the cyclo-  
addition is shown by the disappearance of the  $\lambda_{\max}$   
= 305 nm peak in the UV spectrum. The reaction mixture  
is evaporated in vacuo, on a water bath of 50-60 °C,  
the residual oil is dissolved in 50 ml. of benzene,  
15 washed with 50 ml. of water and subsequently with two  
50-ml. portions of benzene. The benzene phase is dried  
over magnesium sulfate and evaporated in vacuo to yield  
an oily residue. It is then column chromatographed on  
a 30-fold amount of Kieselgel 60 (0.063-0.2 nm), using  
20 a 10 : 1 mixture of benzene and acetone as an eluant.  
The  $R_f > 0.75$  fractions are combined, evaporated and  
column chromatographed again on a 40-fold amount of a  
Kieselgel 60 (0.063-0.2 nm), with a 1 : 1 mixture of  
benzene and chloroform as an eluant. The product obtained  
25 at  $R_f = 0.56$  is isolated.

Yield: 8.5 g. (0.0257 moles), 13 % based on the starting  
3-ethyl-pyridine.

t.l.c. (Kieselgel 60  $F_{254}$ , eluant: 10 : 1 benzene/acetone,

$R_f = 0.312$

1 : 1 benzene/chloroform

$R_f = 0.56$

development in iodine vapour or in UV light of  
254 nm.

5 IR spectrum (film)  $\text{cm}^{-1}$ : 2300-CN; 1700 N-C=O; 1470 Ph;  
700 Ph.

NMR spectrum ( $\text{CDCl}_3$ ) ppm: 7.3 (5 aromatic H-s); 6.3-6.4  
(d,  $\text{H}_1^5 + \text{H}_1^6$ ); 5.15 (S benzyl  $-\text{CH}_2-$ ); 5.05  
(d,  $\text{H}_1^1$ ).

10 Preparation 3

N-Benzyloxycarbonyl-7-chloro-7-methoxycarbonyl-2-  
azabicyclo[2.2.2]oct-5-ene

118.5 g. (1.5 moles) of absolute pyridine are dis-  
solved in 1000 ml. of absolute methanol, whereupon 57 g.  
15 (1.5 moles) of powdered sodium borohydride are carefully  
added at a temperature below  $-65^\circ\text{C}$ , followed by the  
addition of 248 ml. (298 g., 1.75 moles) of benzyl chloro-  
formate. The reaction is strongly exothermic. When the  
addition is complete, the mixture is stirred for an  
20 additional hour at  $-70^\circ\text{C}$ , and is then carefully heated up  
to room temperature. The evaporation residue is dissolved  
in 400 ml. of ether, and washed with 400 ml. of water,  
100 ml. of a 0.1 N aqueous hydrochloric acid solution and  
subsequently with two additional 100-ml. portions of  
25 water. The pH of the aqueous phase is about 5-6 after the  
extraction. The ethereal phase is dried over magnesium  
sulfate and evaporated.

UV spectrum of the evaporation residue, containing a  
mixture of 1,2- and 1,4-dihydropyridine isomers in methanolic

solution:

$\lambda_{\max}$  = 305 nm 1,2-dihydropyridine,

$\lambda_{\max}$  = 260-270 nm unreacted pyridine,

$\lambda_{\max}$  = 230-240 nm 1,4-dihydropyridine.

- 5           The 248 g. of the evaporation residue obtained are dissolved in 700 ml. of acetonitrile, and 192 g. (1.54 moles) of 2-chloroacrylic acid chloride and 5 g. of hydroquinone are added. The completion of the cycloaddition is shown in the spectrum by the disappearance of the
- 10        $\lambda_{\max}$  = 305 nm peak. Thereafter 400 ml. of methanol are added to the mixture, which is allowed to stand at room temperature for three hours. The pH of the acidic solution is adjusted to 8-9 with triethylamine, under cooling, and it is then evaporated. The evaporation residue is dis-
- 15       solved in 500 ml. of benzene and washed with 100 ml. of water. The benzene phase is dried over magnesium sulfate and evaporated. 442 g. of an oily product are obtained as an evaporation residue, which is chromatographed on a Kieselgel 60 (0.063-0.2 mm) column, using a 10 : 1 mixture
- 20       of toluene and ethyl acetate as an eluant.
- Yield: 95 g. (18.9 %, 0.284 moles)
- Melting point: 85 °C
- t.l.c. (Kieselgel 60 plate, eluant: 10 : 1 benzene/ethyl acetate, development in iodine vapour):  $R_f$  = 0.6
- 25       IR spectrum: 1720  $\text{cm}^{-1}$  ester C=O; 1690  $\text{cm}^{-1}$  lactam C=O.
- NMR spectrum: 2.75 ppm (s-OCH<sub>3</sub>), 5.2 ppm (s, benzyl -CH<sub>2</sub>-), 6.3 ppm (m olephin H-s), 7.4 ppm (aromatic H-s).

Preparation 4N-Benzylloxycarbonyl-7-chloro-7-cyano-2-azabicyclo-  
/2.2.2/oct-5-ene

N-benzylloxycarbonyl-1,2-dihydropyridine, prepared from  
5 15.8 g. (0.2 moles) of pyridine as described in Preparation 3  
is dissolved in 100 ml. of acetonitrile. 34 g. (0.4 moles)  
of  $\alpha$ -chloro-acrylonitrile and 2 g. of hydroquinone are  
added to the solution, which is then stirred at 80 °C for  
30 hours. The completion of cycloaddition is verified by  
10 the disappearance of the peak at  $\lambda_{\text{max}} = 305 \text{ nm}$  in the  
UV spectrum. The reaction mixture is evaporated in vacuo.  
The evaporation residue is dissolved in 150 ml. of benzene  
and washed with 30 ml. of water. The benzene solution is  
dried over magnesium sulfate and evaporated in vacuo. The  
15 crude product is chromatographed on a Kieselgel 60  
(0.063-0.2 mm) column, using a 10 : 1 mixture of toluene  
and ethyl acetate as an eluant.

Yield: 14 g. (23.2 %)

Melting point: 68 °C

20 t.l.c. (Kieselgel 60 plate, eluant: 10 : 1 benzene/ethyl  
acetate, development in iodine vapour):  $R_f = 0.6$

NMR spectrum: 5.2 ppm (s benzyl  $-\text{CH}_2-$ ); 6.5 ppm (m olephin  
H-s), 7.4 ppm. (aromatic H-s).

Preparation 5

25 2-Benzylloxycarbonyl-7-bromo-7-methoxycarbonyl-2-azabicyclo-  
/2.2.2/oct-5-ene

To 40 g. (0.2 moles) of N-benzylloxycarbonyl-1,2-

- dihydropyridine prepared as described in Preparation 3, 38 g. (0.23 moles) of freshly prepared methyl  $\alpha$ -bromoacrylate and 2 g. of hydroquinone are added. The reaction mixture is allowed to stand at room temperature for 48 hours, under protection from light. The completion of the cycloaddition is shown by the disappearance of the  $\lambda_{\text{max}} = 305 \text{ nm}$  from the UV spectrum. The reaction mixture is evaporated to an oily residue in vacuo, on a water bath of 40-50 °C, and extracted from three 40-ml. portions of a benzene/brine mixture. The benzene phase is dried over magnesium sulfate and evaporated in vacuo, whereafter it is column chromatographed on a 30-fold amount of Kieselgel (0.063-0.2 mm), using a 10 : 1 mixture of benzene and ethyl acetate for the elution.
- Yield: 8 g. (0.01 moles), 11 % based on the starting pyridine t.l.c. (Kieselgel 60 F<sub>254</sub>, Merck Art. 5735; eluant: 10 : 1 benzene/ethyl acetate):  $R_f = 0.75$
- IR spectrum (film)  $\text{cm}^{-1}$ : 1740 C=O; 1700 N-C=O, 1405 and 705 monosubstituted phenyl, 1250 -O-CH<sub>3</sub>.
- NMR spectrum (CDCl<sub>3</sub>) ppm: 7.3 [s, Ar(t<sup>5</sup>)]; 6.4 (m H<sup>5</sup>, H<sub>1</sub><sup>6</sup>); 5.2 (benzyl CH<sub>2</sub>); 4.05 (m, H<sub>1</sub><sup>1</sup>) 3.65 (OCH<sub>3</sub> s).

Preparation 67-Chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene hydrobromide

10 g. (0.03 moles) of N-benzyloxycarbonyl-7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene prepared according to Preparation 3 are dissolved in a mixture of 60 ml. of glacial acetic acid and 30 ml. of a 4-5 N solution of hydrogen bromide in glacial acetic acid. The mixture is allowed to stand at room temperature for 10 minutes, and is then evaporated. The evaporation residue is dissolved in 5 ml. of acetone and 300 ml. of ether are added to the solution. The precipitated crystalline material is filtered off.

Yield: 8 g. (94%)

Melting point: 188°C

IR spectrum: 1720  $\text{cm}^{-1}$  ester C=O

NMR spectrum: 3.75 ppm (s -OCH<sub>3</sub>); 6.2-6.5 ppm (olephin H-s).

Preparation 77-Chloro-7-cyano-2-azabicyclo[2.2.2]oct-5-ene hydrogen bromide

5.0 g. (0.0165 moles) of N-benzyloxycarbonyl-7-chloro-7-cyano-2-azabicyclo[2.2.2]oct-5-ene are dissolved in a mixture of 30 ml. of glacial acetic acid and 15 ml. of a 4-5 N glacial acetic acid/hydrogen bromide mixture. The reaction mixture is allowed to stand at room temperature for 10 minutes, and is then evaporated. The evaporation residue is crystallized from acetone.

Yield: 2.0 g. (0.0081 moles) 49 %

Melting point: 224 to 226 °C.

IR spectrum: 2220  $\text{cm}^{-1}$  C  $\equiv$  N

NMR spectrum ( $\text{DMSO}, d_5$ ): 4.5 ppm (d  $\text{H}_1^1$ ); 5.8-6.5 (m  $\text{H}_5^1 + \text{H}_6^1$ ).

5 Preparation 8

4-Ethyl-7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]-  
oct-5-ene hydrobromide

16 g. (0.044 moles) of N-benzyloxycarbonyl-4-ethyl-7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene are dissolved in a mixture of 57 ml. of glacial acetic acid and 114 ml of a 5 N solution of hydrogen bromide in glacial acetic acid. The reaction mixture is allowed to stand at room temperature for a half to one hour. The progress of the reaction is monitored by thin layer chromatography.

15 The mixture is then evaporated in vacuo, on a water bath of 40-50 °C. The obtained oily product is triturated with ether and decanted. The residual oil is chromatographed on a Kieselgel 60 (0.0063-0.2 mm.) column, using a 8 : 4 : 2 mixture of benzene, chloro-

20 form and ethanol as an eluant. The products obtained at  $R_f = 0.1$  and  $R_f = 0.2$ , respectively, are collected. The two products differ in the configuration of the carbomethoxy group.

Yield: 7.2 g. (53 %)

25 t.l.c. (Kieselgel 60  $F_{254}$ ; eluant: 10 : 1 benzene/acetone; development in iodine vapour):  $R_f = 0.6$ .

Under the same conditions, except that the

eluant is a 8 : 4 : 2 mixture of benzene, chloroform and ethanol:  $R_f = 0.1$  and  $0.2$ .

Preparation 9

5 4-Ethyl-7-chloro-7-cyano-2-azabicyclo[2.2.2]oct-5-ene hydrobromide

1 g. of N-benzyloxycarbonyl-4-ethyl-7-chloro-7-cyano-2-azabicyclo[2.2.2]oct-5-ene are dissolved in a mixture of 2 ml. of glacial acetic acid and 0.1 ml. of a 5.3 N solution of hydrogen bromide in glacial acetic acid. The mixture is allowed to stand at room temperature for half an hour, under exclusion of moisture. The mixture is evaporated in vacuo on a water bath of  $40^\circ\text{C}$ , and three-times 20 ml. of acetone and then two-times 10 ml. of methanol are evaporated off. The evaporation residue contains in addition to the desired product also the corresponding acid, obtained by hydrolysis of the cyano group. The two products are separated on a Kieselgel 60 (0.063-0.2 mm.) column, using a 8 : 4 : 2 mixture of benzene, chloroform and ethanol as an eluant.

Yield: 0.1 g. (0.00035 moles, 12 %) of the title compound. t.l.c. (Kieselgel 60  $F_{254}$ ; eluant; a 8 : 4 : 2 mixture of benzene, chloroform and ethanol):  $R_f$  acid = 0.14;

$R_f$  nitrile = 0.44.

25 IR spectrum (KBr)  $\text{cm}^{-1}$ : 3330 NH, 2300  $\text{C}\equiv\text{N}$ .

NMR spectrum ( $\text{CDCl}_3$ ) ppm: 6.1 (m  $\text{H}_1^5 + \text{H}_1^6$ ); 4.2 (d,  $\text{H}_1^1$ ); 1.2 (t ethyl  $\text{CH}_3$ ).

Preparation 107-Bromo-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene hydrobromide

8.0 g. of N-benzyloxycarbonyl-7-bromo-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene are dissolved in 40 ml of dichloromethane, and the solution is saturated with hydrogen bromide gas under cooling for five minutes. After saturation the mixture is allowed to stand for further five minutes, whereupon it is evaporated to yield an oily residue, which is then crystallized from acetone.

Yield: 4.0 g. (0.0125 moles, 60 %).

t.l.c. (Kieselgel 60 F<sub>254</sub>; eluant: a 3 : 4 : 2 mixture of benzene, chloroform and ethanol; development in iodine vapour):  $R_f = 0.55$ .

IR spectrum (KBr)  $\text{cm}^{-1}$ : 1740 C=O; 1250 OCH<sub>3</sub>.

Preparation 116-Chloro-6-methoxycarbonyl-2-azabicyclo[2.2.2]octane hydrobromide

8.5 g. (0.03 moles) of 7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene hydrobromide are dissolved in 85 ml. of methanol. 0.85 g. of a 10 % palladium-on-charcoal catalyst are prehydrogenated in 15 ml. of methanol, and a clear solution of the starting material to be hydrogenated is added in a closed system. Hydrogenation is carried out in a closed system, the progress of the reaction is monitored by measuring the hydrogen consumption. When the calculated amount of hydrogen is

used up, the reaction is terminated. When the reaction is not terminated timely, the reaction proceeds further and the chlorine is replaced by hydrogen. The catalyst is filtered off, the solution is evaporated. A

5 crystalline material is obtained, which is trituated in about 20 ml. of acetone, and allowed to stand overnight in a refrigerator. The precipitate is filtered off on the next day, pulpified with two 5-ml. portions of cold acetone, and dried.

10 Yield: 7 g. (0.0244 moles, 82 %)

Melting point: 181 to 183 °C

#### Preparation 12

N-[2-(3'-Indolyl)-ethyl]-7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene

15 6.0 g. (21.2 mmoles) of 7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene hydrobromide, 6.0 g. (27 mmoles) of tryptophyl bromide and 25 ml. (18.0 g., 0.18 moles) of triethylamine are dissolved in 80 ml. of absolute methanol. The solution is

20 allowed to stand at room temperature for one day. The progress of the reaction is monitored by thin layer chromatography, using a Kieselgel 60 plate, 10 : 2 mixture of toluene and ethyl acetate as an eluant,

- 20 -

and carrying out the development in iodine vapour.

R<sub>F</sub> product: 0.5.

The reaction mixture is evaporated in vacuo.  
To the evaporation residue 300 ml. of ethyl acetate  
5 are added, and the precipitated solid triethylamine  
hydrobromide is filtered off. The mother liquor is  
evaporated. The obtained evaporation residue, which  
is about 7 g. of an oily product, is crystallized from  
a mixture of 50 ml. of ethyl acetate and 2-3 ml. of  
10 n-hexane. The mother liquor of the product is subjected  
to column chromatography on a Kieselgel 60 (0.063-0.2  
mm.) column, using a 10 : 1 mixture of toluene and  
ethyl acetate as an eluant, and the product is  
crystallized from a mixture of n-hexane and ethyl  
15 acetate as described hereinabove.

Yield: 3.5 g. (48.6 %)

Melting point: 128-130 °C

IR spectrum (KBr): 1720 cm<sup>-1</sup> ester C=O, 3400 cm<sup>-1</sup>

indole N-H

20 NMR spectrum, ppm: 7.9 (indole N-H); 7.6 (m aromatic  
H); 6.2-6.5 (m, H<sub>1</sub><sup>5</sup> + H<sub>1</sub><sup>6</sup>); 3.8  
(s -OCH<sub>3</sub>).

#### Preparation 13

N-[2-(3'-Indolyl)-ethyl]-7-chloro-7-cyano-2-azabicyclo-  
25 [2.2.2]oct-5-ene

0.9 g. of tryptophyl bromide are dissolved in  
20 ml. of absolute acetonitrile, and 1.0 g. (0.00403

moles) of 7-chloro-1-cyano-2-azabicyclo[2.2.2]oct-5-ene hydrobromide and 2.4 ml. of absolute triethylamine are added to the solution. The homogenous solution obtained is stirred for 3 days, under exclusion of light and moisture. The progress of the reaction is monitored by thin layer chromatography. On a Kieselgel 60 F<sub>254</sub> plate, using a 10 : 1 mixture of benzene and acetone as an eluant,  $R_f$  tryptophyl bromide is 0.86,  $R_f$  product is 0.76. The reaction mixture is evaporated in vacuo, on a water bath of 30 to 40 °C. The evaporation residue is dissolved in 15 ml. of ether, and extracted with two 5-ml. portions of aqueous ammonia (pH = 10). The ethereal phase is dried over magnesium sulfate, and evaporated in vacuo. The obtained oily product is crystallized from 3 ml. of methanol.

Yield: 0.71 g. (0.002324 moles), 55 %

Melting point: 126 to 128 °C

t.l.c. (Kieselgel 60 F<sub>254</sub>; eluant: 10 : 1 benzene/acetone; development: in UV light of 254 nm or in iodine vapour)  $R_f$  = 0.76

IR spectrum (KBr)  $\text{cm}^{-1}$ : 2300  $\text{C} \equiv \text{N}$ , 3300 indole NH

NMR spectrum ( $\text{CDCl}_3$ ) ppm: 3.8 (d,  $\text{H}_1^1$ ), 6.2-6.8 (m  $\text{H}_1^5 + \text{H}_1^6$ ), 7.05-7.7 (m Ar H + indole  $\text{H}_1^2$ ).

#### Preparation 14

N-[2-(3'-Indolyl)-ethyl]-7-chloro-6-methoxycarbonyl-2-azabicyclo[2.2.2]octane

3.84 g. (0.013 moles) of 6-chloro-6-methoxycarbonyl-2-azabicyclo[2.2.2]octane hydrobromide, 3.05 g. of tryptophyl bromide and 5.55 g. (0.052 moles, 7.6 ml.) of triethylamine are dissolved in 35 ml. of absolute methanol, and the solution is allowed to stand at room temperature for two days. The reaction mixture is evaporated, and to the evaporation residue a mixture of 70 ml. of benzene and 35 ml. of water is added. The organic phase is separated, and washed with two 15-ml. portions of water. The combined aqueous phases are extracted with 15 ml. of benzene. The combined benzene phases are dried over magnesium sulfate, decoloured with charcoal, and evaporated in vacuo. From the evaporation residue 25 ml. of ethanol are eliminated by evaporation, and the residueal solid is crystallized from 3 ml. of ethanol. The mother liquor is evaporated, and the residue is crystallized from isopropanol. Yield: 1.5 g. (0.0043 moles), 33 %.

Preparation 15

20 N-[2-(3'-Indolyl)-ethyl]-4-ethyl-7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene

10.3 g. (0.033 moles) of 4-ethyl-7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene hydrobromide, 7.4 g. (0.033 moles) of tryptophyl bromide and 19 ml. of triethylamine are dissolved in 80 ml. of absolute methanol. The reaction is carried out at room temperature and monitored by thin layer chromatography (Kieselgel 60 F<sub>254</sub> plate) until tryptophyl bromide is completely used

- up, using a 10 : 1 mixture of benzene and acetone as an eluant, and a new product can be detected with a 8 : 4 : 2 mixture of benzene, chloroform and ethanol. The reaction mixture is evaporated in vacuo. To the
- 5 residual oil 100 ml. of water are added, and the obtained mixture is extracted with three 100-ml. portions of benzene. The combined benzene phases are dried over magnesium sulfate, filtered and evaporated. If according to t.l.c. the reaction mixture does not
- 10 contain any decomposition product, the desired product is crystallized from a 96 % ethanol. If the reaction mixture is contaminated with by-products due to decomposition, the crude product is purified by column chromatography.
- 15 Yield: 3.8 g. (1.0 mmole) 31 %  
t.l.c. (Kieselgel 60 F<sub>254</sub>; eluant: 10 : 1 mixture of benzene and acetone and 8 : 4 : 2 mixture of benzene, chloroform and ethanol, resp.; development: in UV light of 254 nm or in iodine vapour):  
20 R<sub>F</sub>: 0.75.
- IR spectrum, cm<sup>-1</sup>: 3300 indole NH, 1720 ester C=O.  
NMR spectrum (CDCl<sub>3</sub>) ppm: 6.2-6.8 (m H<sub>1</sub><sup>5</sup> + H<sub>1</sub><sup>6</sup>),  
7.05-7.7 (m Ar + indole H<sub>1</sub><sup>2</sup>), 3.8 (d H<sub>1</sub><sup>1</sup>).  
Analogously may be prepared N-[2-(3'-indolyl)-ethyl]-7-chloro-7-cyano-4-ethyl-2-azabicyclo[2.2.2]oct-5-ene starting
- 25 with 4-ethyl-7-chloro-7-cyano-2-azabicyclo[2.2.2]-oct-5-ene hydrobromide.

Preparation 16N-(3'-Indolyl)-acetyl-7-6-chloro-6-methoxycarbonyl-2-azabicyclo[2.2.2]octane

7.1 g. of 3-indolyl-acetic acid, 4.2 g. (0.04  
5 moles), 5.75 ml. of triethylamine are dissolved in  
120 ml. of absolute dimethyl formamide. The solution is  
cooled to a temperature between -5 °C and -10 °C, and  
4.8 g. (0.04 moles) 4.9 ml.) of pivaloyl chloride are  
added dropwise, at the same temperature. After stirring  
10 for 20 minutes a thick suspension is obtained, to which  
a solution of 11.4 g. (0.04 moles) of 6-chloro-6-methoxy-  
carbonyl-2-azabicyclo[2.2.2]octane hydrobromide and  
4.2 g. (0.04 moles) of triethylamine in 120 ml. of  
dimethyl formamide is added, between 0 °C and -5 °C.  
15 When the addition is complete, the mixture is stirred at  
room temperature for an additional hour. The precipitated  
solid, which is triethylamine hydrochloride or hydro-  
bromide, is filtered off and washed with a small amount  
of dimethyl formamide. The mother liquor is evaporated  
20 under a vacuum of 10-20 torr, on a bath of 60°C. To the  
evaporation residue 400 ml. of ethyl acetate are added,  
and the mixture is washed with two 40-ml. portions of  
water, 60 ml. of a 5 % sodium bicarbonate solution and

finally 60 ml. of a 20 % sodium chloride solution, dried over magnesium sulfate, and evaporated. The evaporation residue is recrystallized from 300 ml. of ethanol.

- 5 Yield: 9.3 g. (0.026 moles), 65 %  
Melting point: 195-196 °C.

Preparation 17

N-(3'-Indolyl)-acetyl-7-bromo-7-methoxycarbonyl-2-  
azabicyclo[2.2.2]oct-5-ene

- 10 2.2 g. (0.0126 moles) of 3-indolyl-acetic acid are dissolved in 30 ml. of absolute dimethyl formamide. 1.2 g. of triethylamine are added to the solution, which is then cooled to -5 °C to -10 °C. At this temperature 1.6 g. (0.0126 moles) of pivaloyl chloride  
15 are added dropwise, under vigorous stirring. The triethylamine hydrochloride immediately precipitates from the solution. After stirring for 20 minutes a solution of 4.0 g. (0.0126 moles) of 7-bromo-7-methoxy-carbonyl-2-azabicyclo[2.2.2]oct-5-ene hydrobromide  
20 and 1.2 g. of triethylamine in 20 ml. of dimethyl formamide is added. The mixture is stirred at room temperature for an additional hour, and the hydrochloride or hydrobromide of the precipitated triethylamine is filtered off. The mother liquor is evaporated in  
25 vacuo, on an oil bath of 60 °C. The evaporation residue is dissolved in 300 ml. of dichloromethane and washed with 100 ml. of water. The dichloromethane phase is

dried over magnesium sulfate, and evaporated in vacuo.

The evaporation residue is crystallized from acetone.

Yield: 2.0 g. (0.005 moles) 40 %

5 t.l.c. (Kieselgel 60 F<sub>254</sub>, eluant: a 8 : 4 : 2 mixture  
of benzene, chloroform and ethanol, development: in UV  
light of 254 nm or in iodine vapour) R<sub>f</sub> = 0.85

IR spectrum (KBr) cm<sup>-1</sup>: 3250 NH, 1720 ester C=O, 1620

N-C=O

10 NMR spectrum (CDCl<sub>3</sub> + DMSO d<sub>6</sub>) ppm: 7.7-7.3 indole  
aromatic, 6.6 m (H<sub>1</sub><sup>5</sup> + H<sub>1</sub><sup>6</sup>), 5.0 (m H<sub>1</sub><sup>1</sup>).

## Example 1

Methyl 1,3-vinylene-1,3,4,6,7,12b-hexahydro-2H,12H-indolo[2,3-a]quinoliziny-1-carboxylate

- 1 g. ( $3.24 \times 10^{-3}$  moles) of N-[2-(3'-indolyl)-ethyl]-7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene is dissolved in 10 ml. of tert.-butanol and the solution is stirred at boiling temperature ( $83^{\circ}\text{C}$ ) for 24 hours. It is then evaporated in vacuo and chromatographed on a Kieselgel 60 column, using a 8 : 4 : 2 mixture of toluene, chloroform and ethanol as eluant. The obtained mixture of the compounds of the formulae (II) and (III) is subjected to column chromatography on an  $\text{Al}_2\text{O}_3$  column, using a 1 : 1 mixture of ethyl acetate and chloroform as eluant. 0.25 g. ( $9.2 \times 10^{-4}$  moles) of the title compound are obtained as oil which solidifies.

Yield: 28.4 %.

IR(KBr): 3340 (indole NH), 1720 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.55-7.0 (m, 4H, aromatic H-s)

6.32-6.05 (d, 2H, olefin H-s)

3.95 (br, 3H,  $\text{OCH}_3$ ) ppm.

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\text{C}_1$  (57.59s),  $\text{C}_2$  (40.24t),  $\text{C}_3$  (40.24d),

$\text{C}_4$  (45.41t),  $\text{C}_6$  (50.29t),  $\text{C}_7$  (17.54t),

$\text{C}_{7a}$  (110.74s),  $\text{C}_{7b}$  (127.2s),  $\text{C}_8$  (118.02d),

$\text{C}_9$  (121.83d),  $\text{C}_{10}$  (119.37d),

$\text{C}_{11}$  (111.24d),  $\text{C}_{11}$  (131.76s), C

$\text{C}_{12a}$  (136.01s),  $\text{C}_{12b}$  (55.09d),  $\text{C}_{13}$  (134.95d),

$\text{C}_{14}$  (132.3d) ppm.

MS m/e/80 °C: 308(10,M), 243 (4.4), 241 (5.0), 220(46.0),  
200(3.0), 184 (35.0), 256(17.0) %.

Example 2

Methyl 3a,4,6,7,12b,12c-hexahydro-3H,12H-indolo[2,3-g7-  
5 cyclopent[7a]indolizine-2-carboxylate

1 g. ( $3.24 \times 10^{-3}$  moles) of N-2-(3'-indolyl)-ethyl-7-  
7-chloro-7-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene  
is dissolved in 10 ml. of n-butanol and the solution is  
stirred at 110 °C for 5 hours. The progress of the  
10 reaction is monitored by thin layer chromatography.  
The reaction mixture is evaporated in vacuo, and chromato-  
graphed on a Kieselgel 60 column, using a 8 : 4 : 2  
mixture of toluene, chloroform and ethanol as eluent.  
Yield: 0.47 g. (53 %)

15 IR(KBr): 3320 (indole NH), 1720 (C=O)  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.55-7.0 (m, 4H, aromatic H-s)

6.25 (d, 1H, olefin.)

3.95 (s, 3H,  $\text{OCH}_3$ ) ppm

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\text{C}_1$  (149.8d),  $\text{C}_2$  (112.7s),  $\text{C}_3$  (39.6t),

20  $\text{C}_{3a}$  (41.4d),  $\text{C}_4$  (45.8t),  $\text{C}_6$  (50.29t),

$\text{C}_7$  (17.54t),  $\text{C}_{7a}$  (110.7s),  $\text{C}_{7b}$  (127.2s),

$\text{C}_8$  (118.02d),  $\text{C}_9$  (121.83d),  $\text{C}_{10}$  (119.37d),

$\text{C}_{11}$  (111.2d),  $\text{C}_{11a}$  (131.76s),

$\text{C}_{12a}$  (136.02s),  $\text{C}_{12b}$  (62.6d),  $\text{C}_{12c}$

25 (56.9d) ppm.

MS m/e: 308 (10 M), 243 (1.4), 241 (1.5), 220 (2.8),

200 (4.3), 184 (100), 169 (3.9) %.

## Example 3

Methyl 3a,4,6,7,12b,12c-hexahydro-3H,12H-indolo-  
2,3-g7cyclopent[7a]indolizine-2-carboxylate

0.25 g. of methyl 1,3-vinylene-1,3,4,6,7,12b-  
 5 hexahydro-2H,12H-indolo[2,3-a7quinoliziny]l-1-carboxy-  
 late, prepared as in Example 1 [Compound of formula (II)]  
 are dissolved in 12 ml. of toluene and boiled (111 °C)  
 for 3 hours. The end-product is isolated from the  
 reaction mixture as described in Example 2. The physical  
 10 characteristics of the product obtained are identical  
 with those given in Example 2.

Yield: 0.19 g. (76 %)

## Example 4

2-Cyano-3a,4,6,7,12b,12c-hexahydro-3H,12H-indolo[2,3-g7-  
 15 cyclopent[7a]indolizine

1 g. ( $3.2 \times 10^{-3}$  moles) of N-[2-(3'-indolyl)-ethyl]-  
 7-chloro-7-cyano-2-azabicyclo[2.2.2]oct-5-ene is dis-  
 solved in 1.5 ml. of diethylene glycol at 80 °C, and  
 the solution is stirred at 160 °C for 20 minutes. The  
 20 progress of the reaction is monitored by thin layer  
 chromatography. The reaction mixture is cooled to 20 °C,  
 diluted with 15 ml. of acetone and the product obtained  
 is isolated in a crystalline form (melting point:  
 234 to 237 °C).

25 Yield: 0.2 g. (22 %)

IR (KBr): 3320 (indole NH), 2230 (CN)  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$  + DMSO): 7.77-7.1 (m, 4H, aromatic H-s)

6.85 (d, 1H, olefin)

4.1 (d, 1H, N-CH)

3.65 (m, 1H, CH adjacent olefin) ppm

$^{13}\text{C}$  NMR. ( $\text{CDCl}_3$  + DMSO):  $\text{C}_1$  (149.8d),  $\text{C}_2$  (114.8s),

5  $\text{C}_3$  (39.6t),  $\text{C}_{3a}$  (41.4d),  $\text{C}_4$  (45.8t),

$\text{C}_6$  (57.1d),  $\text{C}_7$  (17.6t),  $\text{C}_{7a}$  (106.77s),

$\text{C}_{7b}$  (126.97s),  $\text{C}_8$  (117.91d),  $\text{C}_9$  (121.07d),

$\text{C}_{10}$  (118.72d),  $\text{C}_{11}$  (110.99d),  $\text{C}_{11a}$

(133.54s),  $\text{C}_{12a}$  (136.37s),  $\text{C}_{12b}$  (62.6d),

10  $\text{C}_{12c}$  (56.8d) ppm.

MS m/e: 276 (10.1), 275 (23 M), 274 (6), 185 (23),

184 (100), 183 (11), 169 (7) %.

#### Example 5

Methyl 3-ethyl-3a,4,6,7,12b,12c-hexahydro-3H,12H-indolo-

15 /2,3-g/cyclopent/a/indolizine-2-carboxylate

1g. of N-2-(3<sup>4</sup>-indolyl)-ethyl-7-chloro-7-methoxy-carbonyl-4-ethyl-2-azabicyclo[2.2.2]oct-5-ene is dissolved in 20 ml. of methanol, and the solution is refluxed under nitrogen.

The progress of the reaction is monitored by thin layer chromatography. When the total amount of the starting material is used up, the reaction mixture is evaporated in vacuo, and the oily product is chromatographed on a Kieselgel 60 chromatographic column, using a 8 : 4 : 2 mixture of 20 benzene, chloroform and ethanol as eluant. The product is crystallized from a 96 % ethanolic solution of 25 sulfuric acid in the form of its sulfate salt.

Melting point: 285 to 288 °C

Yield: 0.3 g. (37 %)

IR (KBr): 3340 (indole NH), 1720 (C=O)  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.65-7.0 (m, 4H, aromatic H-s)

5 6.95 (d, 1H, olefin )

3.8 (d, 1H, CH-N)

0.9 (t, 3H,  $\text{CH}_2\text{-CH}_3$ ) ppm

MS m/e: 336 (M 13), 335 (2.3), 321 (2.9), 305 (46), 184  
(100), 169 (5.2) %

10 Example 6

2-Cyano-3-ethyl-3a,4,6,7,12b,12c-hexahydro-3H,12H-indolo-  
2,3-g7cyclopent7a7indolizine

1 g. ( $2.85 \times 10^{-3}$  moles) of N-7(3-indolyl)-  
ethyl7-7-chloro-7-cyano-4-ethyl-2-azabicyclo2.2.2oct-5-  
15 ene is dissolved in 20 ml. of n-butanol, and the solution  
is refluxed for 6 hours. The progress of the reaction is  
monitored by thin layer chromatography. When the total  
amount of the starting substance is used up, the mixture  
is evaporated in vacuo, and the obtained oily product  
20 is subjected to column chromatography as described in  
Example 5.

Yield: 0.2 g. (23 %)

IR (KBr): 3340 (indole NH), 2230 (CN)  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.78-7.13 (m, 4H, olefin H-s)

25 6.9 (d, 1H, olefin.)

3.75 (d, 1H, CH-N)

0.9 (t, 3H,  $\text{CH}_2\text{-CH}_3$ ) ppm.

MS m/e: 303 (12M), 302 (2.5), 288 (2.7), 272 (48),  
184 (100) %

Example 7

5 Methyl 1,3-ethylene-1,3,4,6,7,12b-hexahydro-2H,12H-indolo[2,3-a]quinoliziny-1-carboxylate

0.1 g. ( $2.88 \times 10^{-4}$  moles) of N-[2-(3'-indolyl)-ethyl]-7-6-chloro-6-methoxycarbonyl-2-azabicyclo[2.2.2]octane are dissolved in 1 ml. of diethylene glycol. at 190 °C, and the solution is stirred for 20 minutes. The  
10 product obtained is separated by column chromatography as described in Example 5 (eluant: 8 : 4 : 2 mixture of toluene, chloroform and ethanol), isolating the product obtained at  $R_f=0.62$ .

Melting point: 148 to 151 °C

15 Yield: 0.03 g. (33.5 %)

IR (KBr): 3320 (indole NH), 1720 (C=O)  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.55-7.0 (m, 4H, aromatic H-s)

3.85 (s, 3H,  $\text{OCH}_3$ ) ppm.

20  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\text{C}_1$  (52.83s, 34.57t),  $\text{C}_3$  (36.12d),  
 $\text{C}_4$  (51.94t),  $\text{C}_6$  (50.61t), 17.01t),  
 $\text{C}_{7a}$  (109.65s),  $\text{C}_{7b}$  (127.39s),  
 $\text{C}_8$  (118.02d),  $\text{C}_9$  (121.66d),  $\text{C}_{10}$  (119.37d),  
 $\text{C}_{11}$  (111.24d),  $\text{C}_{11a}$  (132.7a),  $\text{C}_{12a}$   
(135.95s),  $\text{C}_{12b}$  (t1.55d),  $\text{C}_{13}$  (28.65t),  
25  $\text{C}_{14}$  (36.56t) ppm

MS m/e: 310 (58. M); 309 (100), 295 (2), 279 (3.3), 259  
(0.5), 251 (2), 239 (1.5), 223 (1.9), 211 (15),  
135 (7), 187 (7), 182 (10) %

## Example 8

Methyl 1,3-vinylene-1,3,4,6,7,12b-hexahydro-2H,12H-indolo[2,3-a]quinolizine-6-one-1-carboxylate

- 1 g. ( $2.5 \times 10^{-3}$  moles) of N-(7-indolyl)-acetyl-7-bromo-7-methoxycarbonyl-2-azabicyclo[2,2,2]oct-5-ene is dissolved in 40 ml. of dry dichloromethane. To this solution a solution of silver tetrafluoroborate in benzene is added under continuous stirring, and the mixture is stirred at room temperature. The progress of the reaction is monitored by thin layer chromatography. The inorganic compounds are eliminated from the reaction mixture with 5 ml. of a saturated sodium bicarbonate solution, the organic phase is dried, evaporated in vacuo, and the components are separated by column chromatography as described in Example 5 and isolated as a colourless oil.
- IR (film): 3400 (indole NH), 1720 (C=O), 1600 (N-C=O)  $\text{cm}^{-1}$
- $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.55-7.07m, 4H, aromatic H-s)  
 6.32-5.81 (d, m, 2H, olefin)  
 5.23-4.71 (t and 2xm, 2H, N-CH<sub>2</sub>-)  
 3.81 (s, 3H, OCH<sub>3</sub>) ppm
- $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): C<sub>1</sub> (60.56s, 43.19t), C<sub>3</sub> (39.54d), C<sub>4</sub> (49.90t), C<sub>6</sub> (169.92s), C<sub>7</sub> (29.25t), C<sub>7a</sub> (106.79s), C<sub>7b</sub> (126.69s), C<sub>8</sub> (118.45d), C<sub>9</sub> (122.88d), C<sub>10</sub> (119.83d), C<sub>11</sub> (116.16d), C<sub>11a</sub> (125.23s), C<sub>12a</sub> (136.59s), C<sub>12b</sub> (59.25d), C<sub>13</sub> (136.97d), C<sub>14</sub> (130.05d) ppm.

MS m/e: 322 (45.M), 305 (6), 291 (4), 198 (80), 185 (10),  
184 (52), 170 (100), 169 (86), 115 (11) %.

Example 9

Methyl 1,3-ethylene-1,3,4,6,7,12b-hexahydro-2H,12H-  
5 indolo[2,3-a]quinolizine-6-one-1-carboxylate

0.45 g. ( $1.26 \times 10^{-3}$  moles) of N-[7(3-indolyl)-  
acetyl-7-6-chloro-6-methoxycarbonyl-2-azabicyclo[2.2.2]-  
octane are reacted with silver tetrafluoroborate. Then  
the procedure described in Example 8 is followed. The  
10 end-product is isolated as a colourless oil.

IR (film): 3400 (NH), 1700 (C=O), 1600 (N-C=O)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\text{C}_1$  (57.89s),  $\text{C}_2$  (31.88t),  $\text{C}_3$  (36.09d),  
 $\text{C}_4$  (50.23t),  $\text{C}_6$  (168.57s),  $\text{C}_7$  (29.19t),  
 $\text{C}_{7a}$  (107.00s),  $\text{C}_{7b}$  (126.31s),  $\text{C}_8$  (118.43d),  
15  $\text{C}_9$  (122.87d),  $\text{C}_{10}$  (119.94d),  $\text{C}_{11}$  (110.90d),  
 $\text{C}_{11a}$  (125.29s),  $\text{C}_{12a}$  (136.85s),  
 $\text{C}_{12b}$  (63.77d),  $\text{C}_{13}$  (31.15t),  $\text{C}_{14}$  (32.92t) ppm

MS m/e: 324 (100, M), 307 (24), 293 (5.3), 292 (4.3),  
(6.5), 225 (9.4), 199 (11), 198 (15), 184 (8.2),  
20 171 (47) %.

Example 10

2-Cyano-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo-  
[2,3-g]cyclopent[a]indolizine

0.27 g. ( $1 \times 10^{-3}$  moles) of 2-cyano-3a,4,6,7,12b-  
25 hexahydro-3H,12H-indolo[2,3-g]cyclopent[a]indolizine  
are dissolved in 5 ml. of methyl alcohol, and this solution  
is added to a prehydrogenated solution of 0.05 g. of a

10 % palladium-on-charcoal catalyst in 2 ml. of methanol, and hydrogen gas is bubbled through the reaction mixture under vigorous stirring. The progress of the reaction is followed by thin layer chromatography, the catalyst is  
 5 filtered off, washed with methanol and the combined alcoholic phases are evaporated in vacuo to yield 0.25 g. of an oily product.

IR (KBr): 3320 (indole NH), 2230 (CN)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.65-7.05 (m, 4H, aromatic H-s)

10 4.1 (d, 1H, N-CH) ppm

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\text{C}_1$  (40.07t),  $\text{C}_2$  (42.78d),  $\text{C}_3$  (39.65t),  
 $\text{C}_{3a}$  (41.37d),  $\text{C}_4$  (45.85t),  $\text{C}_6$  (50.29t),  
 $\text{C}_7$  (17.57t),  $\text{C}_{7a}$  (110.7s),  $\text{C}_{7b}$  (127.2s),  
 $\text{C}_8$  (118.02d),  $\text{C}_9$  (121.83d),  $\text{C}_{10}$  (119.37d),  
 15  $\text{C}_{11}$  (111.2d),  $\text{C}_{11a}$  (137.72s),  $\text{C}_{12a}$   
 (136.15s),  $\text{C}_{12b}$  (62.47d),  $\text{C}_{12c}$  (56.78d) ppm

MS m/e: 277 (58, M), 276 (66), 252 (2.9), 251 (3), 209  
 (7.5), 184 (100), 169 (11) %

#### Example 11

20 Methyl 1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo-  
 $\angle 2,3\text{-g7cyclopent} \angle \text{a7indolizine-2-carboxylate}$

0.052 g. of methyl 3a,4,6,7,12b,12c-hexahydro-3H,12H-indolo $\angle 2,3\text{-g7cyclopent} \angle \text{a7indolizine-2-carboxylate}$  are reduced as described in Example 10. The obtained product  
 25 is isolated as an oil.

Yield: 0.048 g. (96%)

IR (KBr): 3320 (indole, NH), 1720 (C=O)  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.55-7.05 (m, 4H, aromatic, H-s)

3.95 (s, 3H,  $\text{OCH}_3$ ) ppm

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\text{C}_1$  (39.6t),  $\text{C}_2$  (43.2d),  $\text{C}_3$  (39.85t),

$\text{C}_{3a}$  (41.25d),  $\text{C}_4$  (45.87t),  $\text{C}_6$  (50.35d),

5  $\text{C}_7$  (17.54t),  $\text{C}_{7a}$  (110.76s),

$\text{C}_{7b}$  (127.23s),  $\text{C}_8$  (118.12d),  $\text{C}_9$  (121.83d),

$\text{C}_{10}$  (119.37d),  $\text{C}_{11}$  (111.2d),  $\text{C}_{11a}$

(131.76s),  $\text{C}_{12a}$  (136.02s),  $\text{C}_{12b}$  (62.45d),

$\text{C}_{12c}$  (56.68d) ppm

10 Example 12

Methyl 3-ethyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-a]cyclopent[a]indolizine-2-carboxylate

Essentially the procedure described in Example 10 is followed except that as starting material methyl 3-ethyl-  
15 3a,4,6,7,12b,12c-hexahydro-3H,12H-indolo[2,3-g]cyclopent-  
[a]indolizine-2-carboxylate is employed.

IR (film): 3340 (indole NH), 1720 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.75-7.13 (m, 4H, aromatic H-s)

3.85 (d, 1H, CH-N)

20 0.9 (t, 3H,  $\text{CH}_2\text{-CH}_3$ ) ppm

MS m/e: 338 (90M), 337 (100), 239 (9), 185 (14), 184 (22),  
170 (16), 169 (31) %.

Example 13

2-Cyano-3-ethyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-g]cyclopent[a]indolizine

Essentially following the procedure described in Example 10 but starting from 2-cyano-3-ethyl-3a,4,6,7,12b,12c-

hexahydro-3H,12H-indolo[2,3-g]cyclopent[a]indolizine  
the title compound is obtained.

IR (film): 3340 (indole NH), 2230 (CN)  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.75-7.1 (m, 4H, aromatic H-s)

5 3.70 (d, 1H, CH-N)

0.9 (t, 3H,  $\text{CH}_2\text{-CH}_3$ ) ppm

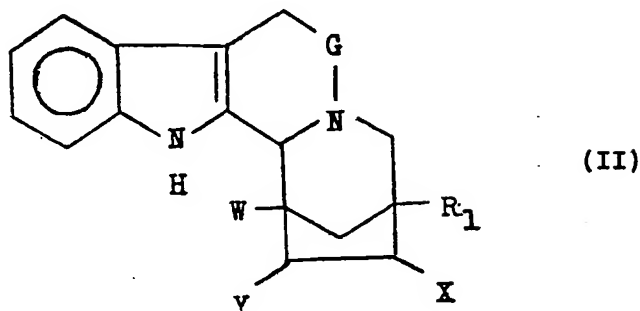
Example 14

Methyl 1,3-ethylene-1,3,4,6,7,12b-hexahydro-2H,12H-  
indolo[2,3-a]quinoliziny1-1-carboxylate

10 Essentially following the procedure described in  
Example 10 but starting from methyl 1,3-vinylene-  
1,3,4,6,7,12b-hexahydro-2H,12H-indolo[2,3-a]quinoliziny1-  
1-carboxylate the title compound is obtained.

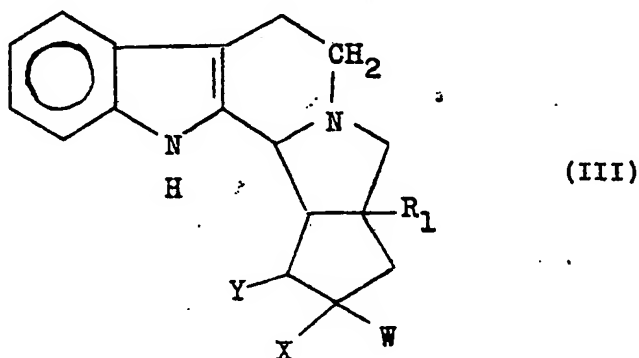
Claims

1. Compounds of formula (II),



in which

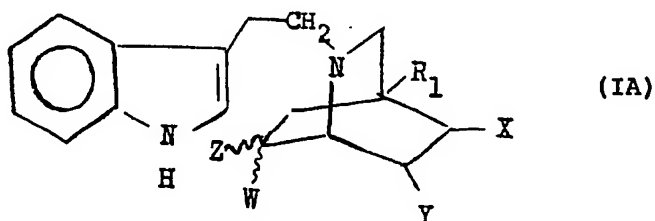
- 5 W is alkoxycarbonyl having from one to four carbon atoms in the alkoxy moiety or cyano,  
 R<sub>1</sub> is hydrogen or alkyl having from one to four carbon atoms,  
 G is a  $>\text{CH}_2$  or  $>\text{C}=\text{O}$  group with the proviso  
 10 that, where G is a  $>\text{C}=\text{O}$  group, W is alkoxycarbonyl having from one to four carbon atoms in the alkoxy moiety and R<sub>1</sub> is hydrogen, and  
 X and Y each stand for hydrogen or together represent a C-C bond.
- 15 2. Compound of formula (III),



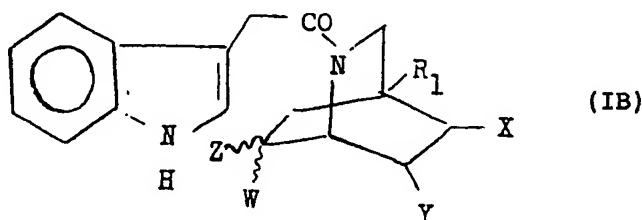
in which W, X and Y are as defined in claim 1.

3. Pharmaceutical compositions comprising as active ingredient, at least one compound according  
 20 to claim 1 or claim 2 in association with a pharmaceutical carrier or excipient.

4. Compounds according to claim 1 or claim 2 for use as gastric acid secretion inhibitors.
5. A process for the preparation of compounds of formula (II) as defined in claim 1 wherein G is a  $\text{>CH}_2$  group and/or of compounds of formula (III) as defined in claim 2 which comprises heating a compound of formula (IA)



- (in which W,  $R_1$ , X and Y are as defined in claim 1 and Z is halogen) in an organic solvent, and, if desired, subsequently separating the mixture of the compounds of formulae (II) and (III) obtained, and/or converting the compound of formula (II) into the corresponding compound of formula (III) whereby the desired product is obtained.
6. A process as claimed in claim 5 in which the organic solvent is a polar aprotic solvent.
7. A process as claimed in claim 5 or claim 6 in which a mixture of the compounds of formulae (II) and (III) is separated by column chromatography.
8. A process for the preparation of compounds of formula (II) as defined in claim 1 wherein G is a  $\text{>C=O}$  group which comprises reacting a compound of formula (IB)



(in which X and Y are as defined in claim 1, W' is (C<sub>1-4</sub> alkoxy)carbonyl and Z is halogen) with a complexing agent in an organic solvent, under anhydrous conditions.

- 5 9. A process as claimed in claim 8 in which the organic solvent is an apolar aprotic solvent.
10. A process for the preparation of compounds of formula (II) as defined in claim 1 or of formula (III) as defined in claim 2, wherein X and Y are
- 10 each hydrogen which comprises subjecting a compound of formula (II) as defined in claim 1 or of formula (III) as defined in claim 3, wherein X and Y together represent a C-C bond to catalytic hydrogenation.

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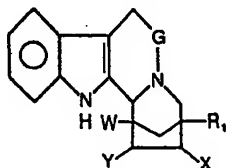
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74 Representative: **Pett, Christopher Phineas et al, Frank B.**  
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54 Indolo 2,3-alquinolizine and indolo 2,3-glycyclopentalindolizine derivatives.

57 Compounds of formulae (II)

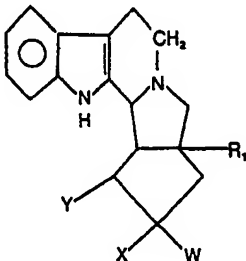


(II)

G is a  $>CH_2$  or  $>C=O$  group with the proviso that, where G is a  $>C=O$  group, W is alkoxycarbonyl having from one to four carbon atoms in the alkoxy moiety and R<sub>1</sub> is hydrogen, and

X and Y each stands for hydrogen or together represent a C-C bond, are disclosed, which compounds possess interesting gastric acid secretion inhibiting activity. Processes for preparing them and pharmaceutical compositions containing them are also disclosed.

and (III)



(III)

wherein

W is alkoxycarbonyl having from one to four carbon atoms in the alkoxy moiety or cyano,

R<sub>1</sub> is hydrogen or alkyl having from one to four carbon atoms,

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**EP 0 130 823 A3**



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# EUROPEAN SEARCH REPORT

0130823

EP 84 30 4487

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
A	US-A-2 975 184 (WARNER LAMBERT) * Column 1, lines 16-51; column 2, lines 12-18 *	1,3	C 07 D 471/18 C 07 D 471/14 A 61 K 31/435// C 07 D 211/82 (C 07 D 471/18 C 07 D 221:00 C 07 D 221:00 C 07 D 209:00 ) (C 07 D 471/14 C 07 D 221:00 C 07 D 209:00 C 07 D 209:00 )
A	US-A-2 908 691 (SEARLE) * Column 1, lines 16-28; column 2, lines 19-28 * -----	1,4	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			C 07 D 471/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 25-06-1985	Examiner ALFARO I.
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